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HILL, KEVIN KAI	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,557	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-53* is/are pending in the application.

4a) Of the above claim(s) *8-12,14,17-19,21,22 and 24-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,13,15,16,20 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *May 16, 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 16, 2008 has been entered.

Election/Restrictions

Applicant has elected with traverse the invention of Group I, claims 1-13 and 15-32, drawn to a method of identifying one or more agents with therapeutic activity to treat one or more symptoms of a disease which is associate with aberrant expression or activity of epithelial sodium channels (ENaC),

Within Group I, Applicant has further elected the restricted subgroup "IA", Claims 1-9, 13, 15-23 and 28-32, drawn to a method of identifying an agent with dual therapeutic activity in mammalian cells.

Within Group IA, Applicant has elected the following species:

i) the physiological agent category, antibiotic, as recited in Claim 16,

ii) the physiological agent compound , doxil, as recited in Claim 20. Upon further examination of the subject matter, the Examiner has extended the species to include doxorubicin.

iii) the cellular functionality, wherein the agent modulates transcription of a molecule that regulates ENaC transcription, as recited in Claim 23,

iv) the virus type, adeno-associated virus, as recited in Claim 4,

v) the selected transcriptional agent activity, wherein the agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC, as recited in Claim 7, and

vi) the mammalian cell type species, human, as recited in Claim 15.

Amendments

Applicant's response and amendments, filed May 16, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claim 3, withdrawn Claims 8-12, 14, 17-19, 21-22 and 24-53, and amended Claims 1-2, 7, 13, 15-16, 20 and 23.

Claims 8-12, 14, 17-19, 21-22 and 24-53 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-2, 4-7, 13, 15-16, 20 and 23 are under consideration.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the May 16, 2008 response will be addressed to the extent that they apply to current rejection(s).

Priority

Applicant's claim for the benefit of a prior-filed application parent provisional applications 60/459,323, filed March 31, 2003 and 60/512,347, filed October 16, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on May 16, 2008. The Examiner was able to consider these to the extent of time allowable. The signed and initialed PTO Forms 1449 are mailed with this action.

Specification

1. **The prior objections to the disclosure are withdrawn** in light of Applicant's amendments to the specification and/or arguments provided, wherein Applicant has addressed trademarked "Miglyol", replaced the term "DF*" with "ng/mL" in Table 2, and argues that the terms "doxorubicin" and "doxyrubicin" are synonymous, and that the active ingredient in DOXIL® is doxorubicin. Furthermore, in the context of the particular data disclosed in the specification (*in vitro* versus *in vivo*), the use of "DOX" in the specification is clear. As DOXIL® is likely not bioavailable to culture cells, any response to "DOX" in cells *in vitro* would necessarily not be a response DOXIL®, e.g., the "DOX" employed to generate the data in Figures 5 and 7-10 was clearly not DOXIL®, as the data was obtained using airway epithelial cells, i.e., the data was obtained from cells *in vitro*. The data in Figure 6 was obtained after intranasal administration of rAAV and Z-LLL and doxorubicin (see page 78). Note that *in vivo* DOXIL® administration is mentioned in the Examples on pages 73-76 (referring to Figures 1 and 3), then on pages 100-101 (where doxorubicin and DOXIL® are each referred to).

Moreover, regardless of the "DOX" formulation, the active agent in those formulations is doxorubicin.

Claim Objections

2. **The prior objection to Claims 13, 15-16, 20 and 23 under 37 CFR 1.75(c)** as being in improper form **is withdrawn** in light of Applicant's amendments to the claims.

3. **Claim 2 is objected to because of the following informalities**: the phrase "the ENaC activity" (line 9) should read "the increased ENaC activity" so as to be concordant with the "increased expression or activity" of line 5, thereby obviating any confusion or lack of antecedent basis regarding the specific, e.g. increased or decreased, ENaC activity that is being referred to.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. **The prior rejection of Claims 1-2, 4-7, 13, 15-16, 20 and 23 under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's amendments to the claims to recite a step that actually accomplishes the preamble and to remove the trademarked product.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. **Claims 1-2, 4-7, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the office action mailed November 14, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed May 16, 2008.

With respect to claim 1, and claims dependent thereon, the claimed invention is directed to a method to identify one or more agents with dual therapeutic activity, the method comprising

the step of selecting one or more agents which inhibits expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease or increase [modulate], directly or indirectly, the level or amount of transcription of one or more subunits of ENaC.

With respect to claim 2, and claims dependent thereon, the claimed invention is directed to a method to identify one or more agents with dual therapeutic activity, the method comprising the step of selecting one or more agents which enhances the transduction of a viral gene therapy vector, wherein said agent that enhances the transduction of a viral gene therapy vector also possesses the functional property of decreasing or increasing [modulate], directly or indirectly, the level or amount of transcription of one or more subunits of ENaC.

At issue for the purpose of written description requirements is the lack of written description for those agents possessing the required functional properties and those mammalian cells having aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000).

In analyzing whether the written description requirement is met for agent genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, doxorubicin is the only species whose complete structure is disclosed to possess the functional property of inhibiting the expression of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of the ENaC γ-subunit. The specification discloses that doxorubicin increases the CpG methylation of the γ-ENaC gene promoter (pg 15, Figure 11; pg 93, lines 7-30). It is noted that the specification discloses that it is not known if doxorubicin inhibits long-term ENaC activity through increases in α- or β-ENaC subunit promoter CpG methylation (pg 96, line 19), as required by claim 23.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that agent may be, but is not limited to, those agents that inhibit transcription of one or more ENaC subunit genes, alter the level, amount or activity of a molecule that alters ENaC transcription, alter ENaC RNA stability, and/or alter the trafficking and processing of molecules, for instance, molecules

of non-viral origin through intracellular compartments, including without limitation proteasomes, endosomes, and trans-Golgi, and/or through the cytosol, e.g., via cytoskeletal components such as microtubules or microfilaments. In one embodiment, the agent is not an antagonist of ENaC. In another embodiment, the agent is not an agent that binds a cell membrane bound protein, e.g. ENaC or the receptor for hepatocyte growth factor. In yet another embodiment, the agent is not an agent that alters post-translational processing of ENaC. In another embodiment, the agent is not a gene of, or a gene product encoded by, a mammalian genome, e.g., a protein encoded by a mammalian cell, the complement of the gene, or a portion of the gene or its complement, e.g., an antisense oligonucleotide (pg 4, lines 12-27).

However, the specification does not disclose any identifying characteristic as to how an artisan would have identified and differentiated one structurally and functionally distinct compound that possesses any one of such properties from another compound that might possess such properties. It is noted that all these agents vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

In analyzing whether the written description requirement is met for the genus of mammalian cells having increased expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, it is first determined whether a representative number of species have been described by their complete structure.

However, neither the specification nor the art teach the objective, quantitative values to determine whether the expression or activity of the α, β and γ ENaC subunits is increased in the enormous genus of mammalian cell types embraced by the claims. Regulation of ENaC activity can occur at different levels, i.e. transcription, translation, translocation and degradation, as well as single-channel open probability and conductance. ENaC subunits [α, β and γ] have been shown to be transcriptionally up-regulated by aldosterone, a low sodium diet or dexamethasone in the kidney, colon and lung, in a tissue- and subunit-specific fashion (Audige et al, Clinical Sci. 104:389-395, 2003; pg. 390, col. 1, ¶2). Using quantitative, real-time polymerase chain reaction (QT-PCR), Audige et al sought to establish whether ENaC is transcriptionally regulated in nephrotic syndrome, and whether expression of ENaC subunit mRNAs and/or protein expression correlates with the profile of urinary sodium excretion using the experimental model of PAN-induced nephrotic syndrome in the rat. Audige et al found that mRNA levels of the α, β and γ ENaC subunits fluctuated over the course of the experiment, first increasing, then decreasing, having escaped regulation by aldosterone, and that the changes in mRNA levels are not paralleled by the amount of ENaC subunit protein expression, e.g. the abundance of βENaC or γENaC protein did not significantly change throughout the study (pg 393, col. 2, Protein Expression and Discussion). Although significant sodium retention occurred from days 5 to 7 in the presence of high plasma aldosterone concentrations, ENaC mRNAs normalized and protein levels of ENaC subunits remained unchanged (pg 394, col. 1, ¶1).

Similarly, Bubien et al (J. Biol. Chem. 276(11): 8557-8566, 2001) teach that when comparing human lymphocytes from Liddle's disease patients and non-Liddle's disease patients, the Liddle's disease lymphocytes were 2.5 times more fluorescent than non-Liddle's cells when

stained for expression of ENaC (pg 8562, col. 1, Immunohistochemical Analysis). However, the authors were unable to ascertain if the increased fluorescence was due to an increase in the amount of ENaC expressed on the cell surface or an increase in the number of exposed epitopes, because the exact number of epitopes and stoichiometry is not known. Bubien et al were unable to provide quantitative values of mRNA or protein expression of the α, β and γ ENaC subunits. ENaC is expressed in the kidney, colon, lung, retina and salivary gland.

The expression of ENaC subunits along the respiratory epithelium is complex and varies between species (Kellenberger et al, Physiological Review 82:735-767, 2002; pg 739, col. 1, Lungs). However, sodium channels, neither known nor contemplated by Applicant yet embraced by the claims, are still being identified in the art and thus the objective states of activity and how such genes are regulated is simply not known. The art teaches that "[O]ur knowledge regarding the structure and function of these [ENaC and ASIC] channels is still emerging and needs to be improved (Kellenberger et al; pg 760, col. 1, Perspectives). Even within the contemplated ENaC α, β and γ genes, the breadth of aberrant expression or activity of these genes is not fully described in the art because the art has not identified quantitative measurements to objectively determine what is "aberrant", especially with respect to the enormous genus of mammalian cell types embraced by the claims.

While the claim recites that the increased ENaC activity is relative to corresponding cells with a wildtype CFTR, neither the claims nor the specification establish a nexus between expression levels of ENaC and wildtype CFTR. As discussed above, the art already recognizes considerable uncertainty regarding normal vs. aberrant ENaC expression levels. Neither the art nor the specification disclose a predictable correlation between ENaC and wildtype CFTR. Furthermore, the claims embrace an enormous range of expression levels of wildtype CFTR, e.g. poorly transcribed and/or poorly translated CFTR RNA molecules encoding wildtype CFTR protein. Thus, the reference cell type is not adequately described so as to clearly and objectively identify which cell possesses increased expression of ENaC.

One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, does not suffice to define the genus because it is only an indication of what the genus does, rather than what it is. See *Fiers*, 984 F.2d at 1169-71,25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such species of the genus may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re *Wilder,* 736 F.2d 1516,1521,222 USPQ 369,372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally thought to exist, in the absence of knowledge as to what that material consists of, is not a description of that entire material.

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function … does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

The specification fails to disclose sufficient identifying characteristics such as complete structure, partial structure, physical and/or chemical properties, or functional characteristics when coupled with a known or disclosed correlation between function and structure. The art does not teach a recognized or predictable correlation between a compound's structure and its

functional ability to inhibit the expression or activity of ENaC, enhance the transduction of a viral vector, decrease the level or amount of transcription of one or more ENaC subunits, and/or modulate the transcription of one or more molecules that regulates ENaC transcription. While the specification discloses a laundry list of structurally diverse, possible compounds and agents (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3), the specification fails to disclose a representative number of species which would lead one skilled in the art to conclude that the Applicant was in possession of the claimed inventive genera. Rather, the agent species specifically disclosed in practice of the claimed inventions are Z-LLL, LLnL and doxorubicin (e.g. pg 72, lines 7-20), wherein those of ordinary skill in the art would recognize that these few species do not adequately represent the enormous genus of structurally diverse compounds disclosed in the above-mentioned laundry list.

While the specification discloses means for screening compounds that inhibit expression or activity of ENaC or enhance viral transduction, the specification does not disclose a correlation between selective inhibitory or enhancing activity and the structure of a putative inhibitor or enhancer, nor information regarding what structural features would likely be associated with the desired functional properties. While one of ordinary skill in the art would conclude that the Applicant would have been in possession of methods for identifying compounds that inhibit the expression or activity of ENaC, enhance the transduction of a viral vector, decrease the level or amount of transcription of one or more ENaC subunits, and/or modulate the transcription of one or more molecules that regulates ENaC transcription, one of ordinary skill in the art would not conclude that the Applicant would have been in possession of the enormous genus of compounds having the desired activity at the time of filing so as to perform the instantly claimed methods requiring the use of compounds identified by the disclosed screening methods. The practice of the instantly claimed methods to identify compounds with dual activities requires the artisan to select *a priori* a desired structure possessing a desired function, and thus requires prior knowledge of the structures and properties of a compound that would predictably result in the desired activity. However, the number of structures encompassed by the claims is vast and their corresponding properties as per the requirements of the claims are unknown (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3).

Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the genus of agents which inhibit expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease, directly or indirectly, the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector. The one species of agent specifically disclosed, doxorubicin, is not representative of the genus because the genus is highly variant.

Accordingly, given that the specification does not teach what is the complete structure of the agent species of the exceptionally broadly-defined "agent" genus, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the required starting materials, that is a genus of agents which inhibit expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector and/or modulates the transcription of one or molecules that regulates ENaC transcription, to perform the necessary active steps and effect the claimed methods, at the time the application was filed.

Based on the Applicant's specification, the skilled artisan cannot envision what mammalian cell expressing amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC would fall within the metes and bounds of the claims for possessing "increased expression or activity". Accordingly, given that the specification does not disclose the objective, quantifiable levels by which expression or activity is considered "increased", this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the required starting materials, that is a genus of mammalian cells having increased expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, to perform the necessary active steps and effect the claimed methods, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicant argues that it is Applicant's position that agents that enhance viral transduction and methods to identify those agents are well known to the art (see, for example, Duan et al (2000) and Examples 1-2, 4-5 and 7 in the specification). Moreover, methods to detect agents that inhibit expression or activity of ENaC are disclosed in the specification (see Examples 8-9),

and agents for screening in the recited methods are disclosed at pages 4-6 and 27-34, and Examples 1-2 and 4 in the specification (i.e., more than one species is disclosed).

Applicant's argument(s) has been fully considered, but is not persuasive. Whether one of skill in the art could screen for the claimed compounds having the claimed functional properties, i.e. inhibiting the expression or activity of ENaC, enhancing the transduction of a viral vector, decreasing the level or amount of transcription of one or more ENaC subunits, and/or modulating the transcription of one or more molecules that regulates ENaC transcription, is not germane to this rejection, since it is the invention as described in the original specification, and its failure to support the instant claims that is at issue here. An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). In the instant case, while Duan et al may have taught a method to identify agents, the method of identifying such compounds does not immediately describe a compound's structural identity that would sufficiently distinguish it from any other structure that does not possess the required functional property.

Furthermore, while Applicant argues that the claims no longer recite "aberrant", the Examiner respectfully directs Applicant's attention to claim 2, step b, "aberrant expression or activity".

6. **Claims 1-2, 4-7, 13, 15-16, 20 and 23 stand rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the office action mailed November 14, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed May 16, 2008.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claims is exceptionally large for encompassing an enormous genus of agents that inhibit expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α-, β- and γ-subunits of ENaC and/or enhance the transduction of a viral gene therapy vector.

The specification does not define the term "mammal", but discloses a preferred mammalian embodiment that is human (pg 4, lines 1-4). The art recognizes mammals to reasonably encompass some 5,500 species (including Humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21, 2007). The art also recognizes that the mammalian body consists of a large genus of distinctly different organs, e.g. heart, lung, brain, muscle, skin, liver, etc.., and an even larger genus of distinctly different cell types. Thus, the claimed inventions reasonably embrace any mammalian cell type that endogenously possesses, or is transformed with a nucleic acid encoding (pg 4, lines 7-8), an epithelial sodium channel.

The claimed inventions are directed to methods for identifying one or more agents with dual therapeutic activity. At issue for the purpose of enablement requirement is the method step of selecting an agent identified only by it's *a priori* ability to inhibit expression or activity of amiloride epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC and/or enhance the transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription. The specification fails to disclose the ability to

predictably identify the enormous genus of structurally diverse agents possessing functionally diverse properties contemplated in the specification (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3) that would inhibit the expression of ENaC **and** enhance viral transduction.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The method comprises the step of selecting one or more agents which inhibits expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector and/or modulates the transcription of one or molecules that regulates ENaC transcription.

The elected embodiment of the agent is an antibiotic, specifically doxorubicin. The specification discloses that doxorubicin enhances rAAV transduction and increases the CpG methylation of the γ-ENaC gene promoter (pg 15, Figure 11; pg 83, lines 3-4; pg 93, lines 7-30). It is noted that the specification discloses that it is not known if doxorubicin inhibits long-term ENaC activity through increases in α- or β-ENaC subunit promoter CpG methylation (pg 96, line 19), as embraced by claim 1 and required by claim 23.

The specification fails to disclose the necessary guidance to the artisan for choosing *a priori* an agent that inhibits expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC other than doxorubicin, or for choosing *a priori* an agent that enhances the transduction of a viral gene therapy vector.

While the specification discloses that LLnL and Dox are capable of enhancing AAV transduction (Figure 3) and inhibiting transcription of ENaC using the combination of LLnL/Dox (Figure 10), the specification does not disclose other agents that enhance the transduction of a viral gene therapy vector **and** inhibit ENaC expression or activity. Furthermore, the specification fails to disclose a nexus between the structural properties of a compound and its corresponding functional properties. Thus, a first species within the one of the broadly disclosed genera, e.g. a proteasome inhibitor, does not predictably correlate and immediately lead the artisan to identify another species within another one of the broadly disclosed genera, e.g. a food additive.

The State of the Prior Art

While Duan et al teach a screening method to identify agents that enhance AAV transduction, for example, the prior art does not teach predictable methods to identify agents that, at any particular concentration, enhance AAV transduction **and** inhibit the expression or activity of ENaC. Nor does the prior art teach a common chemical structure possessing the functional property of enhancing AAV transduction **and** inhibiting the expression or activity of ENaC that

would guide the artisan to select a plurality of structurally and functionally diverse genera to be likely compounds having the instantly claimed desired properties.

The Level of One of Ordinary Skill and The Level of Predictability in the Art

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, cell biology and virology. Therefore, the level of ordinary skill in this art is high.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Given the absence of definitions and the lack of disclosure, the specification fails to provide the necessary guidance and direction so that an artisan would know *a priori* that a particular agent has the required inherent property of inhibiting expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhance transduction of a viral gene therapy vector, so as to perform the method steps as claimed.

The artisan must perform extensive screening of an enormous genus of compounds to identify an agent that possesses either one of the first select desired property. Of those agents possessing either one of the first select desired property, the artisan must then test whether or not it possesses all of the secondary recited limitations so as to determine whether or not it possesses dual activity. There is no guidance in the prior art or the specification that establishes predictable correlation between the structural and functional properties of a first compound and the structural and functional properties of second compound. Thus, each agent from the broadly disclosed laundry list must be identified by trial and error.

Similarly, the specification fails to provide the necessary guidance and direction so that an artisan would know *a priori* that a mammalian cell possesses the inherent property aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC, so as to perform the method steps as claimed.

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel*. In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Applicant's Arguments

Applicant argues that the claims are directed to methods of screening for agents with a specific second activity. Agents that enhance viral transduction and methods to identify those agents are well known to the art, and the specification discloses. methods to detect agents that inhibit expression or activity of ENaC, and agents for screening in the recited methods. It is well-settled that it is not necessary that a patent Applicant have prepared and tested all the embodiments of his invention in order to meet the requirements of §112. Furthermore, enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." The need, and methodologies required, to carry out extensive synthesis and screening programs to locate biomolecules with particular properties do not constitute undue experimentation.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant's basis refers to the screening of monoclonal antibodies (*Hybritech Inc. v. Monoclonal Antibodies Inc.*, 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986). However, the Examiner respectfully points out that whereas monoclonal antibodies share a common structural and functional property, the laundry list of broadly disclosed genera of the instant application (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3) do not share a common structural and functional property. How would the artisan know *a priori* that a particular agent would possess the functional property of inhibiting the expression or activity of the genus of amiloride-sensitive epithelial sodium channels (ENaC) having α, β and γ subunits of ENaC known, and not yet known, in the art? Sodium channels of the ENaC gene family are still being identified in the art and thus the objective states of activity and how such genes are regulated are simply not known. The art teaches that "[O]ur knowledge regarding the structure and function of these [ENaC and ASIC] channels is still emerging and needs to be improved (Kellenberger et al; pg 760, col. 1, Perspectives). While doxorubicin is disclosed to possess the claimed functional properties, neither the claims, the specification, nor Applicant's amendment provide a nexus between doxorubicin and the enormous claimed genus of agents. In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **The prior rejection of Claims 1, 4-5, 13, 15-16, 20 and 23 under 35 U.S.C. 103(a)** as being unpatentable over Schwarzbach et al (Int. J. Oncology 20: 1211-1218, 2002; *of record), in further view of Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) **is withdrawn** in light of Applicant's argument that Schwarzbach et al do not teach a screening method, which the Examiner finds persuasive.

8. **The prior rejection of Claims 2, 4, 6-7, 13, 15-16, 20 and 23 under 35 U.S.C. 103(a)** as being unpatentable over Schwarzbach et al (Int. J. Oncology 20: 1211-1218, 2002; *of record), in further view of Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) and Johnson et al (Nature Genetics 2: 21-25, 1992) **is withdrawn** in light of Applicant's amendment to the claim that the mammalian cells to have increased ENaC expression or activity as a result of increased transcription of DNA encoding one or more of the ENaC subunits, a limitation that neither Schwarzbach et al, Duan et al nor Johnson et al teach.

9. **Claims 1, 4-5, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; *of record in IDS).

Bruno et al (FEBS Letters 427:241-246, 1998), Patel et al, Mol. Pharmacol. 52(4):658-666, 1997), and Russell et al (PNAS 92:5719-5723, 1995; *of record in IDS) are provided by the Examiner as evidentiary references.

Determining the scope and contents of the prior art.

Duan et al teach a screening method to identify one or more agents with dual activities, the method comprising contacting *in vitro* mammalian cells with one or more agents and a viral gene therapy vector, and identifying an agent from those contacted with the mammalian cells that enhances the transduction of the viral gene therapy vector relative to mammalian cells contacted with the viral gene therapy vector but not contacted with the one or more agents (pg 1575, col. 1 and Figure 2, Effect of Different Chemical Reagents on AAV transduction), wherein viral gene therapy vector is an AAV vector comprising a marker gene (pg 1576, Figure 3), wherein the cells are human bronchial airway [lung] epithelial cells (pg 1574, col. 1, Methods), wherein the proteasome modulating agent, e.g. LLnL, enhanced rAAV transduction of mammalian lung epithelial cells. Based upon the result achieved by the proteasome modulating agent LLnL, Duan et al suggest that proteasome inhibitors increase AAV transduction (pg 1583, col. 2).

Duan et al do not teach the selection of the instantly elected agent embodiment that is doxorubicin. However, at the time of the invention, Kiyomiya et al taught adriamycin (a synonym for doxorubicin) is a proteasome protease inhibitor in the same genus of proteasome inhibitors discussed in Duan et al that enhance rAAV transduction (pg 2470, col. 1).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, cell biology and virology. Therefore, the level of ordinary skill in this art is high.

Neither Duan et al nor Kiyomiya et al teach the selection of an agent which inhibits expression or activity of ENaC, decreases the level or amount of transcription of one or more

subunits of ENaC, or modulates the transcription of one or molecules that regulate ENaC transcription. However, absent evidence to the contrary, nothing non-obvious is seen with the claimed limitations that the agent, specifically doxorubicin, be used at an amount to inhibit or decrease the level or amount of transcription of one or more subunits of ENaC or a molecule that regulates ENaC transcription because prior to the invention, Bruno et al taught that doxorubicin was known in the art to broadly affect the transcriptional machinery, e.g. RNA Polymerase II, the major RNA polymerase responsible for transcribing genes whose RNAs will be translated into proteins, e.g. one or more subunits of ENaC, as well as impairing the function of several known genes at the transcriptional level (pg 245, col. 1, ¶1). Furthermore, doxorubicin has long been recognized in the art to be a DNA-damaging agent (Patel et al), and DNA-damaging agents have long been recognized in the art to enhance AAV transduction in both stationary and dividing cells (Russell et al), wherein those of ordinary skill in the art routinely optimize the concentration of the DNA-damaging agent so as to enhance viral transduction with less cytotoxicity, thereby improving prospects for gene therapy by AAV vectors (Russell et al, pg 5719, Abstract, Introduction; pg 5720, Figure 2; pg 5721, Figure 3). The art had long-recognized doxorubicin to impair and inhibit the cellular transcriptional machinery, e.g. RNA Pol II, and the instant claims do not recite the degree to which the level of transcription is to be modulated or decreased. In light of the art-recognized property that doxorubicin impairs the transcriptional machinery and is a DNA-damaging agent, one of ordinary skill in the art would reasonably expect doxorubicin to inhibit the transcription or activity of one or more subunits of ENaC or one or molecules that regulate ENaC transcription when used at the appropriate concentration.

Thus, absent evidence to the contrary, it is routine for the artisan to vary the effective concentration of a given agent, e.g. a transcriptional inhibitor/DNA-damaging agent such as doxorubicin, so as to achieve the desired result in a desired cell type, e.g. inhibit ENaC expression or activity, and when used at the optimized concentration, to reasonably expect to enhance rAAV transduction because doxorubicin is another species within the genus of proteasome inhibitors **and** DNA-damaging agents recognized in the art to possess AAV transduction enhancement properties.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the proteasome inhibitor agent LLnL as taught by Duan et al with the proteasome inhibitor agent doxorubicin as taught by Kiyomiya et al in a screening method to identify one or more agents with dual activities with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. At the time of the invention, doxorubicin was recognized as another species within the genus of proteasome inhibitors **and** DNA-damaging agents recognized in the art to possess AAV transduction enhancement properties. An artisan would be motivated to substitute the proteasome inhibitor agent LLnL with the proteasome inhibitor agent doxorubicin in a screening method to identify one or more agents with dual activities because Duan et al suggest the investigation of additional agents to enhance AAV transduction (pg 1579, col. 1) and that the use of proteasome modulating agents to enhance AAV gene therapy vectors will provide new approaches for gene therapy of diseases such as cystic fibrosis (Abstract).

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

10. **Claims 2, 4, 6-7, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; *of record in IDS) and Maitra et al (2001; *of record in IDS).

Bruno et al (FEBS Letters 427:241-246, 1998), Patel et al, Mol. Pharmacol. 52(4):658-666, 1997), Russell et al (PNAS 92:5719-5723, 1995; *of record in IDS) and Flotte (2002; *of record in IDS) are provided by the Examiner as evidentiary references.

Determining the scope and contents of the prior art.

Duan et al teach a screening method to identify one or more agents with dual activities, the method comprising contacting *in vitro* mammalian cells with one or more agents and a viral gene therapy vector (pg 1575, col. 1 and Figure 2, Effect of Different Chemical Reagents on AAV transduction), wherein viral gene therapy vector is an AAV vector comprising a marker gene (pg 1576, Figure 3), wherein the cells are human bronchial airway [lung] epithelial cells (pg

1574, col. 1, Methods), wherein the proteasome modulating agent, e.g. LLnL, enhanced rAAV transduction of mammalian lung epithelial cells. Based upon the result achieved by the proteasome modulating agent LLnL, Duan et al suggest that proteasome inhibitors increase AAV transduction (pg 1583, col. 2).

Duan et al do not teach the selection of the instantly elected agent embodiment that is doxorubicin. However, at the time of the invention, Kiyomiya et al taught adriamycin (a synonym for doxorubicin) is a proteasome protease inhibitor in the same genus of proteasome inhibitors discussed in Duan et al that enhance rAAV transduction (pg 2470, col. 1).

Neither Duan et al nor Kiyomiya et al teach the step of contacting *in vitro* mammalian cells having aberrant ENaC expression, wherein the mammalian cells do not express functional CFTR. However, at the time of the invention, Maitra et al taught the step of contacting *in vitro* mammalian cells expressing the ΔF508-CFTR mutation, which results in improper folding and trafficking of the CFTR protein, leading to its degradation in the endoplasmic reticulum by the 26S proteosome machinery of the cell aberrant ENaC expression, with doxorubicin. Maitra et al teach that of the more than 850 individual CFTR mutations leading to the CF phenotype that have been described, the most important is ΔF508 (phenylalanine deletion at amino acid position 508), which is seen in 70% of all CF patients. However, importantly, if this mutant protein is folded and expressed in the membrane, it functions normally as a chloride channel. Moreover, it is estimated that restoration of functional CFTR expression to 10% of normal levels would be sufficient to ameliorate the symptoms of the disease *in vivo*. Thus, there is great interest in development of strategies that can enhance ΔF508-CFTR cell surface expression, which may be clinically useful in treatment of CF patients (pg C1031). Doxorubicin significantly increased functional cell surface expression and activity of CFTR and ΔF508-CFTR.

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and

have the practical experience in molecular biology, cell biology and virology. Therefore, the level of ordinary skill in this art is high.

Those of ordinary skill in the art have long-recognized that recombinant adeno-associated viral vectors are useful as gene therapy vectors, and that cystic fibrosis patients are candidates for gene therapy (Flotte).

Similarly, CFTR has been shown to regulate ENaC (prior art cited in specification pg 1, lines 21-23), and those of ordinary skill in the art have long-recognized that a reciprocal expression relationship between CFTR and ENaC, wherein over-expression of ENaC suppresses CFTR expression and in CF mutant cells, ENaC expression is increased (e.g. Tsang et al, Japanese J. Physiol. 51(4):539-542, 2001; pg 542, col. 1).

Furthermore, doxorubicin had long been recognized in the art to be a DNA-damaging agent (Patel et al), and DNA-damaging agents had long been recognized in the art to enhance AAV transduction in both stationary and dividing cells (Russell et al), wherein those of ordinary skill in the art optimized the concentration of the DNA-damaging agent so as to enhance viral transduction with less cytotoxicity, thereby improving prospects for gene therapy by AAV vectors (Russell et al, pg 5719, Abstract, Introduction; pg 5720, Figure 2; pg 5721, Figure 3). Furthermore, Bruno et al taught that doxorubicin was known in the art to broadly affect the transcriptional machinery, e.g. RNA Polymerase II, the major RNA polymerase responsible for transcribing genes whose RNAs will be translated into proteins, e.g. one or more subunits of ENaC, as well as impairing the function of several known genes at the transcriptional level (pg 245, col. 1, ¶1). The art had long-recognized doxorubicin to affect the cellular transcriptional machinery, and the instant claims do not recite the degree to which the level of transcription is to be modulated. In light of the art-recognized property that doxorubicin impairs the transcriptional machinery and is a DNA-damaging agent, one of ordinary skill in the art would reasonably expect doxorubicin to inhibit the transcription or activity of one or more subunits of ENaC or one or molecules that regulate ENaC transcription when used at the appropriate concentration.

Thus, absent evidence to the contrary, it is routine for the artisan to vary the effective concentration of a given agent, e.g. a transcriptional inhibitor/DNA-damaging agent such as doxorubicin, so as to achieve the desired result in a desired cell type, e.g. enhance rAAV transduction and inhibit ENaC expression or activity, when used at the optimized concentration.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the proteasome inhibitor agent LLnL as taught by Duan et al with the proteasome inhibitor agent doxorubicin as taught by Kiyomiya et al in a screening method to identify one or more agents with dual activities with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. At the time of the invention, doxorubicin was recognized as another species within the genus of proteasome inhibitors **and** DNA-damaging agents recognized in the art to possess AAV transduction enhancement properties. An artisan would be motivated to substitute the proteasome inhibitor agent LLnL with the proteasome inhibitor agent doxorubicin in a screening method to identify one or more agents with dual activities because Duan et al suggest the investigation of additional agents to enhance AAV transduction (pg 1579, col. 1) and that the use of proteasome modulating agents to enhance AAV gene therapy vectors will provide new approaches for gene therapy of diseases such as cystic fibrosis (Abstract).

It also would have been obvious to one of ordinary skill in the art to substitute the human bronchial airway [lung] epithelial cells of Duan et al with mammalian cells having aberrant ENaC expression, wherein the mammalian cells do not express functional CFTR, as taught by Maitra et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute the human bronchial airway [lung] epithelial cells of Duan et al with mammalian cells having aberrant ENaC expression, wherein the mammalian cells do not express functional CFTR because Maitra et al teach that there is great interest in development of strategies that can enhance ΔF508-CFTR cell surface expression, which may be clinically useful in treatment of CF patients (pg C1031), and that doxorubicin significantly increased functional cell surface expression and activity of CFTR and ΔF508-CFTR.

It also would have been obvious to modify the method of Duan et al to comprise a step of assaying the mammalian cells that do not express functional CFTR for decreased or inhibited

ENaC expression or activity with a reasonable expectation of success because those of ordinary skill in the art have long-recognized that a reciprocal expression relationship between CFTR and ENaC, and decreased or inhibited ENaC expression or activity would be an indicator of increased expression of functional CFTR, which would be of therapeutic value for those patients in need.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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